DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

FEBRUARY 2, 1987

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FEBRUARY 2, 1987

The Recombinant DNA Advisory Committee (RAC) was convened for its thirty-sixth meeting at 9:00 a.m. on February 2, 1987, in Building 1, Wilson Hall, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. Mr. Robert Mitchell (Chair), Attorney at Law in California, presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Barbara H. Bowman	Susan K. Gottesman	Jeffrey W. Roberts
Donald C. Carner	Irving S. Johnson	Frances E. Sharples
Don Bert Clewell	Edward L. Korwek	Anne K. Vidaver
Mitchell L. Cohen	Robert E. Mitchell	LeRoy Walters
Bernard D. Davis	Gerald L. Musgrave	William J. Gartland, Jr.
Charles J. Epstein	Paul E. Neiman	(Executive Secretary)
Robert P. Erickson	Joseph S. Pagano	

A committee roster is attached (Attachment).

Ad hoc consultants:

Royston C. Clowes, University of Texas
Gerard J. McGarrity, Coriell Institute for Medical Research
Robert W. McKinney, National Institutes of Health

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

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[1]The RAC is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting agency representatives:

Howard M. Berman, Veterans Administration
Joel M. Dalrymple, U.S. Army Medical Research Institute of Infectious Diseases
George Duda, Department of Energy
Bernard Greifer, Department of Commerce
Phillip Harriman, National Science Foundation
Elizabeth Milewski, Environmental Protection Agency
Henry I. Miller, Food and Drug Administration
Sue A. Tolin, Department of Agriculture
William J. Walsh, Department of State

National Institutes of Health staff:

Marianne Abbs, NIAID
W. French Anderson, NIAID
Stanley Barban, NIAID
Becky Lawson, NIAID
Rachel Levinson, OD
Lynn Ann Lewis, NIAID
Barbara Harrison, OD
Bernard Talbot, NIAID

Others:

Carter Blakey, Federation of American Societies for Experimental Biology
Irene Brandt, Eli Lilly and Company
Dennis Carroll, General Accounting Office
Chia Ting Chen, Department of Labor
Mark Crawford, Science
Isabelle R. Davidson, Pfizer, Inc.
Charles J. Eby, Monsanto Company
Diane Edwards, Science News
Joseph R. Fordham, Novo Laboratories, Inc.
Jeffrey L. Fox
Mary Gant, Office of Science and Technology Policy, Executive Office of the President
Irene Glowinski, U.S. Congressional Staff
Rebecca J. Goldburg, Environmental Defense Fund
Alan R. Goldhammer, Industrial Biotechnology Association
George H. Irwin, Monsanto Agricultural Company
Dorothy Jessup, Department of Agriculture
Peter L. Joseph, Department of Agriculture
Attila T. Kadar, Food and Drug Administration
John H. Keene, Abbott Laboratories
Patricia W. Kener, Monsanto Company
Lori Lamore, Commerce Clearing House
Alvin G. Lazen, National Academy of Sciences
David F. Long, Veterinary Biologics Consultant
A. S. Lubiniecki, Genentech, Inc.

Jack J. Manis, Upjohn Company
James H. Maryanski, Food and Drug Administration
Margaret Mellon, Environmental Law Institute
David Moore, Association of American Medical Colleges
Phil Musi, Blue Sheet
Robert B. Nicholas, Blum, Nash, and Railsback
Michelle Owings, Burditt, Bowles, Radzius
Harvey S. Price
Jeremy Rifkin, Foundation on Economic Trends
Edward Lee Rogers, Attorney, Washington, D.C.
Alex Samofal, Department of Agriculture
Mark Segal, Environmental Protection Agency
Valerie P. Setlow, Office of the Assistant Secretary for Health
Janet Shoemaker, American Society for Microbiology
David E. Smolin, American Cyanamid Company
Cynthia L. Spencer, Cooper Laboratories, Inc.
Clarence E. Styron, Monsanto Company
William Szkrybalo, Pharmaceutical Manufacturers Association
Charles Turbyville, NIH Week
Joseph Van Houten, Schering-Plough Corporation
Winona Wagner, E. I. Du pont De Nemours & Company
John Whalen, National Institute of Occupational Safety and Health
David Wheeler, Chronicle of Higher Education
Doug Yarrow, British Embassy
Stephanie Zobrist, Embassy of Switzerland

I. CALL TO ORDER AND INTRODUCTORY REMARKS

Mr. Mitchell, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 9:00 a.m., February 2, 1987. He said the meeting was called pursuant to Federal Register notice of December 19, 1986, which being 30 or more days prior to today's date met the NIH Guidelines for Research Involving Recombinant DNA Molecules requirements. He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to adjourn at approximately 4:00 p.m.

Mr. Mitchell noted that with new appointments the RAC now was at full membership with 25 members and requested Dr. Gartland to ascertain whether a quorum was present. Dr. Gartland stated that a quorum was present, and Mr. Mitchell declared that the committee could proceed with business.

Mr. Mitchell noted that he intended to make every effort to abide by the distributed agenda with respect to time estimates for each item of business and added there were four items on the agenda which, having been duly published in the Federal Register 30 or more days prior to the meeting date, the RAC could take official action on at this meeting.

He then reminded the committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; ad hoc consultants to the RAC; NIH staff members; members of the public who had submitted written documents; and finally, other members of the public. He underlined that RAC was advisory to the Director of NIH and that in light of this persons with minority opinions should voice them so as to provide Dr. Wyngaarden with the entire spectrum of RAC opinions on a given topic. Mr. Mitchell then told the committee that in all voting he would call first for the affirmative, then for the negative, and finally for abstentions, and underlined that if any voting member felt compelled to abstain due to conflict of interest that such member should notify the Chair so that the record could duly reflect such.

Mr. Mitchell then made note of Mailings I and II which were sent to members prior to the meeting. He also noted that materials that had been recently received were supplied at the table for each member.

Mr. Mitchell then introduced three new members of RAC who were present at the meeting: Mr. Donald C. Carner, Dr. Don Bert Clewell, and Dr. Robert P. Erickson. He briefly outlined each new member's background and affiliations and stated that he and other members of the committee welcomed them and looked forward to their contributions on the committee.

Mr. Mitchell then announced that three ad hoc members were in attendance at the meeting: Dr. Royston Clowes of the University of Texas, Dr. Robert McKinney of the NIH, and Dr. Gerard McGarrity of the Coriell Institute for Medical Research. He briefly touched on their professional expertise and welcomed their participation.

II. MINUTES OF THE MEETING OF SEPTEMBER 29, 1986

Mr. Mitchell then called upon Dr. LeRoy Walters to review the minutes of the September 29, 1986, meeting of the RAC (tab 1288). Dr. Walters said he had read the minutes and found them clear and complete; however, he felt some minor grammatical corrections should be made, not affecting the substance of the minutes, and he offered to take these up later with the Office of Recombinant DNA Activities (ORDA) staff.

Dr. Bowman stated she had reviewed the minutes and moved that they be accepted. Dr. Davis asked whether such motion would allow for the grammatical corrections which Dr. Walters would recommend, and Mr. Mitchell said small stylistic changes not affecting the substance would be allowable under the current motion.

Mr. Mitchell then put the motion to a vote. The motion passed unanimously with two members abstaining.

Mr. Mitchell then stated that in light of the number of pertinent comments received after Mailings I and II had gone out, that it be appropriate for the RAC to take a short recess to allow members time to review fully these comments. Mr. Mitchell then recessed the committee for a half hour prior to discussion of the next agenda item.

III. REPORT OF THE WORKING GROUP ON DEFINITIONS AND PROPOSED REVISION OF SECTION III-A-2 OF THE NIH GUIDELINES

Mr. Mitchell reconvened the meeting at 9:45 a.m. and stated that this agenda item would include a discussion of materials contained in tabs 1285, 1286, 1288, and 1289. He further stated that an additional comment had just been handed to members which was received from the American Society for Microbiology. He said that in light of the Federal Register notice being published 30 or more days prior to this meeting, that the RAC could take final action on this agenda item today and that discussion would be broken into two parts with Dr. McGarrity leading off the discussion.

Dr. McGarrity stated that ORDA had asked the RAC Working Group on Definitions to examine the two terms "recombinant DNA" and "deliberate release" into the environment. The working group met

on September 5, 1986, and a report of that meeting was made to the RAC at the September 29, 1986, meeting. At that time, the RAC had voted to refer the matter back to the working group for further discussion. He noted that the RAC, during the same meeting, had approved a motion to modify Section III-A-2 dealing with environmental release.

Dr. McGarrity stated that the working group had met on December 5, 1986, and the minutes of that meeting were contained at tab 1285. He reported the first proposal to the RAC from the working group (endorsed by a vote of 10 in favor, 1 opposed, and 1 abstention) was to revise Section III-A-2 of the NIH Guidelines to read in its entirety as follows (tab 1286/II):

> "Deliberate release into the environment of any organism containing recombinant DNA, except those listed below. The term 'deliberate release' is defined as a planned introduction of recombinant DNA-containing microorganisms, plants, or animals into the environment.
>
> "a. Introductions conducted under conditions considered to be accepted scientific practices in which there is adequate evidence of biological and/or physical control of the recombinant DNA-containing organism. The nature of such evidence is described in Appendices L, M, N, and O.
>
> "b. Deletion derivatives not otherwise covered by these Guidelines.
>
> "c. Organisms covered in exemption III-D-2."

Dr. McGarrity then stated the intent of the working group was that Appendix L, referred to in the proposed wording, would be the current Appendix L dealing with plants, with future changes to be recommended by RAC. Appendices M, N, and O would be parallel sections, yet to be written, covering respectively animals, microorganisms other than those used in vaccines, and vaccines.

Dr. McGarrity reported that the working group unanimously approved a motion that:

> "Investigators in the field of vaccine development be apprised of the options for exemption from RAC review as specified in paragraph two of Section III-A, and that a working group be organized to develop criteria and procedures for inclusion in an Appendix O (Vaccines) of Section III-A-2."

Dr. McGarrity said a revised Section III-A-2 had been recommended by the RAC at its September 29, 1986, meeting although it still had not been acted upon by Dr. Wyngaarden. He noted differences between the wording recommended at the September 1986 meeting and the proposed language above. He said a multidisciplinary effort will be needed to develop Appendices M, N, and O.

Dr. McGarrity said in closing that regardless of RAC's action on this proposal that he strongly urged "that an immediate effort be made to develop standards for the environmental issues surrounding vaccines developed by recombinant techniques."

Dr. Gottesman said she felt the proposal included changes which were significant in setting up a structure for including Appendices M, N, and O. However, even if the proposed changes were to be made part of the NIH Guidelines, nothing would change in the review of specific applications until the actual text of Appendices M, N, and O was written. A RAC working group would formulate Appendices M, N, and O, and then put these out for public comment. Before becoming part of the NIH Guidelines, the RAC would review the proposed text of the appendices. She stated that a vote in support of the new proposed Section III-A-2 is thus basically a vote in support of a concept with a chance to subsequently review the actual text of the appendices. The second sentence of the proposed Section III-A-2 is an attempt to get more substance into the term "deliberate release" and to indicate that it should not have a pejorative connotation. Sections b. and c. of the proposed Section III-A-2 are identical to recommendations voted on by RAC at the previous meeting and under consideration by Dr. Wyngaarden. She said she favored the revision of Section III-A-2 of the NIH Guidelines proposed by the working group.

Dr. Korwek asked how this proposed change in Section III-A-2 found at tab 1286/II related to a further change in Section III-A-2 found at tab 1286/III. Drs. Gottesman and Talbot pointed out that the RAC proposed certain changes in Section III-A-2 at the previous RAC meeting. Tab 1286/II proposes certain additional changes, and RAC should consider this first. Tab 1286/III proposes further changes, and this will subsequently be considered.

Dr. Sharples reminded the RAC she had voiced considerable objection to the changes in Section III-A-2 recommended by the RAC at its September 29, 1986, meeting and clarified that her remarks today were not to be taken as referring to those changes; she had not changed her mind regarding her objections to those changes. In regard to the further changes proposed in tab 1286/II, she stated she had no objection to the incorporation of the term "planned introduction" to describe or amplify what constitutes a "deliberate release." However she said that she

personally did not think this wording does much to improve or clarify concepts. She said there were two conceptual points with regard to deliberate release that needed to be spelled out: (1) that deliberate release is of concern if other organisms will be exposed to the organism being released and that this exposure might be harmful; and, (2) that deliberate release is of concern if the organism that is being released will have the opportunity to exchange genetic information with other organisms that are in the environment. She said that adding the words about "planned introduction" did nothing to clarify these concepts. This wording "is not a definition; it is just a description."

Dr. Sharples said that with Appendices M, N, and O not yet being in existence the referencing of such appendices in the NIH Guidelines was unacceptable. She had no objection to an effort being made to create these appendices and felt their construction would represent real progress in the area. However, she felt it would take some time to accomplish this. In regard to Dr. McGarrity's statement that a multidisciplinary effort would be needed to complete these appendices, Dr. Sharples agreed and said she hoped all relevant scientific disciplines would be represented in the working groups convened to work on the appendices. Further, as a member of the Public Affairs Committee of the Ecological Society of America, she said she was certain the society would be willing to assist NIH and the RAC working groups by providing expertise available from within its membership.

Dr. Sharples then called attention to the existing Appendix L which states that:

> "Appendix L specifies conditions under which certain plants, as specified below, may be approved for release into the environment. Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, review by the Plant Working Group and specific approval by NIH."

Dr. Sharples said that for experiments meeting the Appendix L criteria, it is not that these experiments will not be reviewed, but that the Plant Working Group instead of the full RAC would review them. For Appendices M, N, and O, she urged use of the same concept of working group approval in lieu of full RAC approval.

Dr. Vidaver indicated she supported the working group's proposal, and that many of Dr. Sharples' concerns could be covered in the appendices. She said Appendix L was already in place, and the USDA is considering Appendices M and N.

Dr. Clowes said he fully supported the working group's proposal.

He would like to see it extended even further. Rather than specifically citing only exemption III-D-2, he would like all organisms which are already exempt from the NIH Guidelines for laboratory work to also be exempt for deliberate release to the environment. This would then include all recombinations made between organisms that freely exchange genetic material in nature and thus where nothing new is likely to arise from the recombinant DNA technique.

Dr. Gottesman said that Dr. Sharples had pointed out that Appendix L currently provides for review by the RAC Plant Working Group in lieu of the full RAC. She said that in writing the new Appendices M, N, and O, "you could imagine putting into those appendices some mechanisms whereby a proposed experiment would revert to the laboratory experimentation level, some that would require working group review and some that would continue to come before the entire RAC." She felt that an important part of constructing the new appendices would be to decide what the appropriate mechanism should be for dealing with any particular class of "deliberate release" experiment.

Dr. Gottesman then moved that the RAC accept the proposed revision of the NIH Guidelines as contained in tab 1286/II. Dr. Epstein seconded the motion.

Dr. Korwek noted Dr. Sharples' objections to the revision were on the basis that Appendices M, N, and O were not in place. However, he replied that the status quo was not being changed in that even were the proposed reference to these appendices added to the NIH Guidelines, the approval process for any deliberate release experiment would not change until the actual text of the appendices was incorporated into the NIH Guidelines.

Dr. Davis then made a motion to remove from tab 1286/II the following sentence: "The term 'deliberate release' is defined as a planned introduction of recombinant DNA-containing micro-organisms, plants or animals into the environment." He said this sentence did not add anything to the understanding of what is meant by "deliberate release."

Dr. Walters seconded the motion so that discussion of this motion could take place. Dr. Johnson said he felt the wording should be looked at in an historical context in that at the last meeting the RAC asked the Working Group on Definitions to look again at this wording. The working group had come to agreement that the RAC is concerned with planned experiments. Therefore, the words "planned introduction" were appropriate. Further, he added that the votes in the working group on this issue were virtually unanimous resulting in this wording being a consensus of the working group.

Mr. Mitchell then put Dr. Davis' motion to a vote. The motion

was rejected by a vote of 2 in favor, 11 opposed, and 4 abstentions.

Mr. Mitchell then called for further discussion on Dr. Gottesman's original main motion. Mr. Lee Rogers, attorney for the Foundation on Economic Trends and Jeremy Rifkin, said the status quo was not being maintained. He saw this as allowing a change in the NIH Guidelines to go forward anticipating the development of satisfactory appendices. In the absence of the appendices, the amended language was "not workable because of the lack of flesh on the body."

Dr. McGarrity replied that this was a setting up of a superstructure of how environmental releases would be judged in the future. From a practical standpoint it would be better to have the superstructure and mechanisms approved now. He noted that the revision of Section III-A-2 which had been recommended at the September 29, 1986, RAC meeting had still not been finally approved by Dr. Wyngaarden. Therefore, if this revision today were to be recommended, it would undoubtedly be a matter of several months before the NIH Director would act on it, thereby allowing time for development of Appendices M, N, and O.

Dr. Sharples asked about the status of the revision recommended at the previous RAC meeting. Dr. Talbot stated that NIH staff had prepared an environmental assessment (EA) at Dr. Wyngaarden's request. However, the Director was not fully satisfied with that EA and had requested that further information be put in the EA. The revised EA should be resubmitted to the Director soon. Subequent to Dr. Wyngaarden's approval of the EA, a Federal Register notice promulgating the change in the NIH Guidelines would be prepared for his review and approval.

At this point, there being no further discussion on the motion, the motion to recommend the NIH Guidelines changes at tab 1286/II was put to a vote. The results of the voting were 16 in favor of the motion, none opposed, and one abstention. Mr. Mitchell thanked Dr. McGarrity and the members of the Working Group on Definitions for their fine work on this proposal.

IV. PROPOSED REVISION OF SECTION I-B OR SECTION III-A-2 OF THE NIH GUIDELINES

Mr. Mitchell called on Dr. McGarrity to explain the proposal (tab 1286/III). Dr. McGarrity said the Working Group on Definitions considered the term "recombinant DNA." The working group agreed with the concept that certain types of recombinant DNA experiments which do not involve the introduction of foreign DNA need not be subjected to special regulation as "recombinant DNA." The working group was split as to whether it preferred dealing with this problem by changing the definition of recombinant DNA or by further modifications of other sections of the NIH

Guidelines (e.g., those in Section III-A-2). Therefore, the working group presented two options for public comment and RAC consideration.

Dr. McGarrity said the working group had overwhelmingly favored Option 2 as published in the Federal Register as the preferred choice by a vote of 9 in favor, 1 opposed, and no abstentions. Dr. McGarrity added that he felt perhaps the working group's choice had been swayed by an opinion offered by a lawyer on the working group that to change the definition was more radical than changing other portions of the NIH Guidelines. Dr. McGarrity reviewed the major changes proposed in the two options. Dr. Gottesman reviewed some of the public comments received on the two options. She pointed out that option one would eliminate from RAC review certain human gene therapy experiments but that option two would leave review of such experiments within the purview of RAC.

Drs. Korwek, Sharples, Clowes, and Cohen all said they preferred Option 2 to Option 1.

Dr. Neiman said that at the previous RAC meeting he had stated that rearrangements, deletions, and amplifications within higher organisms that do not rapidly change their genomes are not necessarily as innocent as those that occur in microorganisms. Therefore, he felt that modification of Section III-A-2 of the NIH Guidelines would be a more favorable approach than a change in the definition of "recombinant DNA."

Dr. Korwek moved that further consideration of Option 1 be rejected, and Dr. Epstein seconded the motion. Mr. Mitchell called for discussion on the motion and called on Dr. Henry Miller from FDA. Dr. Miller said FDA's view was that the purpose of the NIH Guidelines was to circumscribe a unique or special set of experiments and organisms that required some special attention, not necessarily due to risk involved, but due instead to the use of recombinant DNA in cases which did not occur naturally or were special in some other way. Because of this, Option 1 is preferred. Option 1 would say that it isn't simply cutting and ligating that defines recombinant DNA in a meaningful way; rather it is the joining of heterologous DNAs. He said that changing the definition of "recombinant DNA" right up front was clearer than altering it by changing exemptions.

Dr. Davis agreed with Dr. Miller. He felt it would better guide the courts in making it clear that even if recombinant DNA technology was used, that in our judgment no recombinant DNA existed unless heterologous segments were introduced into the genome. This would appropriately shift emphasis from the procedure to the product. The basic issue is whether the product contains foreign DNA. He said he could not vote for Option 1 as written because the use of the word "organism" in the proposed

footnote was ambiguous and should be replaced by the word "genome."

Dr. Cohen said that the prime concern had always been whether you had the potential to create something unique. One method is to create unique things by mixing genomes, but another is to accelerate the rate of evolution many thousand-fold.

Dr. Clowes said he would rather leave the definition vague and then exempt certain classes rather than trying to build everything into the definition.

Dr. Johnson said he had somewhat the same problems with the Option 1 footnote as Dr. Davis in the use of the words "organism" and "strain"; he said it was unclear whether "organism" and "strain" refers to organisms at the genus or species level.

There being no further discussion on the motion to reject Option 1, Mr. Mitchell called for a vote. The motion carried by a vote of 11 in favor, 6 opposed, and no abstentions.

After a brief summary of the specific changes in language encompassed in Option 2, Dr. Walters moved that Option 2 be adopted. Dr. Neiman seconded the motion.

Mr. Mitchell asked for discussion on the motion. Mr. Rogers referred to comments by the Ecological Society of America which had concern that intergeneric manipulations could pose serious ecological threats. He asked for further discussion on this issue.

Dr. Gottesman said this had been discussed at the previous meeting and was so noted in the minutes. No one had said that all deletions and rearrangements were innocuous. She saw the RAC's mandate as concentrating on unique recombinant DNA constructs. It is not clear that deletions, rearrangements, amplifications, and single base changes should fall under this mandate.

Dr. Epstein asked whether these now to be excluded releases would be reviewed by any agency other than NIH. Mr. Rogers said that was also his concern, i.e., that intergeneric transfers would not be reviewed by anyone and further that the NIH had the most experience in this type of review.

Dr. Sharples explained to Mr. Rogers that intergeneric transfer was not the issue in this proposal, but rather that self-cloning mechanisms, such as deletions and rearrangements within the same organism, were the basic issue. Further, Dr. Sharples said that she believed Dr. Gottesman's view of the RAC's mandate was incorrect; RAC has a duty to make certain that experimental research using recombinant DNA technology is carried out in such

a way as to protect the public and the environment from harm whether or not "foreign" DNA is involved.

Dr. Margaret Mellon from the Environmental Law Institute asked for clarification of the relationship of the NIH Guidelines to the evolving role of the USDA.

Dr. Talbot responded by saying that the USDA had been using the NIH Guidelines. In the June 26, 1986, "Coordinated Framework," they had published their own guidelines for public comment which were modelled after the NIH Guidelines. A subsequent Federal Register notice said that in lieu of separate USDA Guidelines, USDA would propose new provisions relating to agricultural research for inclusion in the NIH Guidelines.

Dr. Sue Tolin said that the USDA indeed had relied on the NIH Guidelines but "we see the need to get some additional things into it. The approaches that are being discussed in terms of developing Appendices L, M, N, and O will certainly go a long way towards those and we plan to be working very closely with NIH on those areas." She also added that not only does USDA sponsor research, but they also have statutory regulatory authority.

Dr. Gottesman said that scientists involved in genetic research other than recombinant DNA technology would be selecting strains with deletions or rearrangements which they may wish to introduce into the environment. If they wish to introduce such strains into the environment this would have to be dealt with by regulatory agencies. An organism engineered by recombinant DNA technology to produce these same deletions and rearrangements should require no more and no less regulation merely because of the process used to arrive at the same end product. Removing the extra layer of RAC and NIH review still leaves the standard review by the regulatory agencies.

Dr. Cohen agreed that there was no need for RAC or NIH review of rearrangements or deletions in microorganisms, but said with higher organisms you are dealing with something different. Dr. Davis said it was a case of probabilities. He felt the probability of making a bacterium more dangerous by deletion or rearrangement was exceedingly low. He felt this was not necessarily the case with viruses, although there were other mechanisms to ensure safety of virus vaccines. He said that unnecessary review of safe experiments could be very expensive and time-consuming.

Dr. Walters said that he seemed to be hearing two separate concerns, one concern for eukaryotes and one concern for microorganisms. He asked what the risks were with higher organisms that were not adequately covered by some other mechanism. If there are no major concerns about higher organisms, then the only thing left to debate is environmental

release of microorganisms containing deletions and rearrangements.

Dr. Gottesman summarized the major changes in tab 1286/III/Option 2, as compared to what had previously been recommended by RAC as: extension to include "single base changes" in part b; and extension to include chromosomal as well as extrachromosomal rearrangements in part c.

Dr. Johnson said he was still concerned with the use of the word "organism" as to whether it referred to genus or species. He proposed an amendment to the wording of Section III-A-2-c, to substitute the word "species" for "strains."

Mr. Mitchell asked for a second on the motion. There being no second for the motion the motion died.

Dr. Davis said he had objection to the word "organism" in the same section, and he would move to have it replaced with the word "species." Dr. Gottesman seconded the motion.

Dr. Griefer from the Department of Commerce said that in his opinion changing the language at this point would be denying public comment on it. Dr. Talbot said that in the past the NIH Director had accepted changes suggested at RAC meetings, sometimes based on public comment, but that major broadening at this stage would not be acceptable without a new opportunity for public comment. He said that the change being contemplated, namely substituting the word "species" for "organism," was in his view a minor clarification and should not have to be resubmitted for public comment.

Mr. Mitchell then called for a vote on amending the language in Section III-A-2-c to read:

> "Rearrangements and amplifications within a single genome. Rearrangements involving the introduction of DNA from different strains of the same species would not be covered by this exemption."

The motion to amend passed by a vote of 16 in favor, none opposed, and 1 abstention.

Mr. Mitchell asked for further discussion on the motion as amended. Dr. Neiman requested amplification on Dr. Gottesman's point as to whether if an experiment could be performed utilizing standard genetic techniques, this should be viewed differently when performed utilizing recombinant DNA technology.

A lengthy discussion took place during which it was argued that there was no difference. Depending on the possible hazard to the

environment and to humans, there may be cause to not allow environmental release of such an organism. This evolved into a debate as to whether plants, bacteria, viruses, or animals should be treated differently in this regard with many opinions being expressed. Finally, Mr. Mitchell asked that over the luncheon recess Dr. Epstein meet with other members of the RAC to formulate an amendment which could be considered by the committee after the luncheon recess. Whereupon, Mr. Mitchell recessed the committee for lunch, to reconvene at 1:30 p.m.

Mr. Mitchell reconvened the committee at 1:30 p.m.

Mr. Rogers said that other agencies do not have complete jurisdiction, so there will not be complete coverage without NIH retaining jurisdiction. He suggested instead of NIH "abrogating its responsibility" that "lesser levels of review" be put into place for those types of experiments that in RAC's opinion do not warrant full committee review.

Dr. Rebecca Goldburg of the Environmental Defense Fund also said the question of risk should be evaluated whether the organism in question existed in nature or not. She supported Mr. Rogers' proposal of some level of review for all releases.

Dr. Clowes said that RAC was created to oversee experiments done with recombinant DNA which could create novel genotypes and not to deal with organisms extant in nature.

Dr. Epstein proposed amended wording for the first sentence of the proposed Section III-A-2-c to read:

> "For extrachromosomal elements and microorganisms (including viruses), rearrangements and amplifications within a single genome."

The rest of this paragraph would remain unchanged from the version at tab 1286/III/Option 2, with the exception of the substitution of the word "species" for "organism" which had already been voted upon and amended.

Dr. Sharples asked whether this change was substantive enough to force resubmission to the Federal Register for public comment. Dr. Talbot said he did not believe so, since this was constricting the exemptions not broadening them. In the past, the NIH Director had accepted those kinds of restrictive changes made by the RAC.

Dr. Tolin asked why plants and animals were being restricted since she felt there was a larger body of knowledge concerning genetically altered plants and animals than altered microorganisms. Dr. Miller agreed.

Dr. Walters reminded the committee that what was being considered only was referring to a small class of deliberate release experiments.

Mr. Rogers again brought up the issue of public comment on this proposed change. Dr. Talbot explained that what was being contemplated by Dr. Epstein's proposed change was a constriction of exemptions, a tightening of the NIH Guidelines, as compared to what was published in the Federal Register at tab 1286/III/Option 2/part c. This would result in fewer exemptions from RAC oversight. In the past, the NIH Director has accepted such RAC changes without additional public comment.

There being no further discussion, Dr. Epstein's amendment for modification of Section III-A-2-c was put to a vote by Mr. Mitchell. The motion was passed by a vote of 11 in favor, 4 opposed, and 1 abstention.

At this point, Mr. Mitchell called for a vote on the main motion, i.e., to recommend modification of Section III-A-2 of the NIH Guidelines as it appeared in the Federal Register at tab 1286/III/Option 2 with Dr. Epstein's amendment of Section III-A-2-c. The motion passed with a vote of 15 in favor, one opposed, and no abstentions.

V. PROPOSED AMENDMENT OF SECTIONS I-A AND III-A OF THE NIH GUIDELINES

Dr. Johnson said he favored this proposal (tabs 1283, 1286/I) which would eliminate the requirement for concurrence by the NIH Office of Recombinant DNA Activities for approval of an experiment approved by another Federal agency. He said it is consistent with the new Federal coordination effort. He stated he believed there may be exclusions over which the RAC may want to continue to maintain jurisdiction such as the human gene therapy.

Dr. Korwek said he supported the proposal. However, he felt there was a problem in the wording of the proposal which deals with "approval" by other agencies in that some agencies do not approve certain requests but merely do not object to them. He cited Investigational New Drug (IND) applications which the FDA does not approve but which become effective for lack of FDA objection. He added the EPA does much the same in their PMN process where after 90 days with no agency objection the manufacturer may proceed.

Dr. Davis said he supported the proposal since he was eager not to see bureaucratic restrictions proliferate and not to have multiple levels of review. In regard to Dr. Korwek's problem with the word "approval", Dr. Davis offered the suggestion that perhaps "clearance" would be a better word. Dr. Korwek said that

he had alternative language which he would propose after further discussion of the proposal.

Dr. Sharples said that the NIH up to this point has been collecting information on a wide variety of things and at this point is a repository of information regarding recombinant DNA technology. She asked if this change in submittal policy might not cause the NIH in future years to have to reconstruct a system to collect the information which it may not possess if this proposal is put in place and the NIH is bypassed.

Dr. Talbot said that today many applications from industry are going directly to EPA or FDA without NIH having any information concerning them. Individuals desiring information can go directly to each of the relevant agencies and ask what they have approved.

Dr. Walters said he agreed with the thrust of the proposal as he believed it of value to eliminate duplication in coordination among Federal agencies. However, the proposal should be modified to retain RAC oversight of human gene therapy. Therefore, he proposed the following additional language be added at the end of the proposed text:

> "However, any experiment that involves the administration of gene therapy to human subjects (see Section III-A-4 of the NIH Guidelines) may not proceed without prior review by the NIH Recombinant DNA Advisory Committee and NIH approval."

He said that since the RAC and the NIH have made such a strong commitment to public review for NIH funded human gene therapy experiments that it would be unwise to withdraw that commitment at this point. Dr. Epstein seconded the motion.

Dr. Miller stated that the FDA strongly supported the proposal but would object to Dr. Walters' amendment in that, "...especially in human gene therapy there is an even greater acute need to avoid reduplication of reviews and delays than in other areas...." He said human gene therapy proposals will be reviewed by the local Institutional Review Boards (IRBs) and by the FDA and that going through the Human Gene Therapy Working Group and and the full RAC would be an extra layer of bureaucracy. He said that when a need for rapid approval has been necessary, such as in anti-AIDS therapeutics, the FDA has managed to react and approve these very quickly, some within a week of submission.

Dr. Walters pointed out that over the last 2 1/2 years the RAC has consistently made the judgment that there are important reasons to bring human gene therapy proposals before the RAC for

public discussion and review; FDA consideration of these proposals will not be public.

Mr. Mitchell asked Dr. Talbot if an investigator proposing to do human gene therapy would have his choice under the proposal to submit the experiment for approval to NIH or to the FDA. Dr. Talbot replied that under the proposal, as published in the Federal Register at tab 1286/I, an investigator submitting such a proposal to FDA would not have to submit it to NIH. However, Dr. Talbot said that he supported Dr. Walters' proposed amendment to require RAC review and NIH approval. Dr. Korwek commented that there was no question that such a proposed experiment would have to be brought to FDA but that the issue was whether it should be brought before the RAC.

Mr. Mitchell re-read Dr. Walters' amendment before putting it to a vote. The motion passed by a vote of 12 in favor, one opposed, and 3 abstentions.

Mr. Mitchell then called for further discussion on the main proposal. Dr. Korwek proposed an amendment to reword the second sentence of the proposal to read:

> "Once approval, or other applicable clearances, have been obtained from a Federal agency other than the NIH (whether the experiment is referred to that agency by the NIH, or sent there directly by the submitter), the experiment may proceed without the necessity for NIH review or approval."

He explained the purpose of this would be to take into account the situation in which an agency does not "approve" an application but merely does not oppose it as in the IND situation that was discussed earlier. Dr. Davis seconded the motion.

Dr. Margaret Mellon asked about cases which are within NIH's jurisdiction, and where USDA judges them to be outside of its jurisdiction. Dr. Talbot stated that in such a case the USDA would not give approval if they said it was out of its jurisdiction and this proposed paragraph in the NIH Guidelines would not be applicable since there would be no approval or clearance from USDA.

Mr. Mitchell then called for a vote on the proposal as amended. The amended proposal is to delete a paragraph from Section III-A of the NIH Guidelines and add at the end of Section I-A of the NIH Guidelines the following:

> "Any recombinant DNA experiment which according to these guidelines requires

approval by the National Institutes of Health (NIH), may be sent by the submitter to the NIH or to another Federal agency that has jurisdiction for review and approval. Once approval, or other applicable clearances, have been obtained from a Federal agency other than the NIH (whether the experiment is referred to that agency by the NIH or sent directly there by the submitter), the experiment may proceed without the necessity for NIH review or approval. However, any experiment that involves the administration of gene therapy to human subjects, (see Section III-A-4 of the Guidelines) will not proceed without prior review by the NIH Recombinant DNA Advisory Committee and NIH approval."

The proposal was put to a vote and the result of the voting was 17 in favor, none opposed, and no abstentions.

VI. PROPOSED REVISIONS OF APPENDICES C-II, C-III, AND C-IV TO THE NIH GUIDELINES

Mr. Mitchell then asked Dr. McKinney to discuss the proposal (tabs 1284, 1286/IV) made by Dr. Frank Young, Commissioner of FDA, to revise Appendices C-II, C-III, and C-IV of the NIH Guidelines.

The proposal is to delete the following language from these Appendices:

"For these exempt laboratory experiments, BL1 physical containment conditions are recommended.

"For large-scale (LS) fermentation experiments BL1-LS physical containment conditions are recommended. However, following review by the IBC of appropriate data for a particular host-vector system, some latitude in the application of BL1-LS requirements as outlined in Appendix K-II-A through K-II-F is permitted."

And substitute:

"For these exempt laboratory experiments, the appropriate physical containment conditions need be no greater than those for the host organism unmodified by recombinant DNA techniques.

"For large scale (LS) fermentation experiments, the appropriate physical containment conditions need be no greater than those for the host organism unmodified by recombinant DNA techniques."

Dr. McKinney reviewed some of the written comments that had been received on this proposal and noted that some contained alternative language to the proposal. Dr. McKinney asked to be placed on record as opposing the adoption of the portion of the proposed language which refers to laboratory level experiments in that BL1 requirements represent nothing more than good laboratory practices and are not restrictive.

As far as the application of BL1-LS in large-scale production of exempt organisms, Dr. Young had referred in his letter to manufacturers who utilized conditions of at least BL1-LS "to ensure compliance with the NIH Guidelines." Dr. McKinney noted that these manufacturers were not obligated to comply with the NIH Guidelines and that even in complying with the NIH Guidelines the recommendation to use BL1-LS is just that, a recommendation.

In closing, Dr. McKinney stated he felt the proposed amendment by Dr. Young dealing with large-scale fermentation did not offer any advantage over present language and suggested the RAC reject the proposal.

Dr. McGarrity said he had come to a different conclusion than Dr. McKinney. He stated the word "latitude" could be interpreted many different ways. IBCs may interpret it differently, and Dr. Young's proposal clarifies this in a more objective manner. Further, he felt the fact that this proposal came from the Commissioner of FDA does carry some weight in that he is the chief regulator in this whole area.

Dr. Cohen suggested the proposal be split in two. For the first part dealing with laboratory experiments, no change, in his view, was necessary since BL1 conditions are simply good laboratory practice. However, with respect to large-scale, he agreed that the wording "some latitude" is not really helpful to the IBCs. He said he would like to see the terminology reworded for large-scale production to encourage modifications appropriate to the degree of safety required.

Dr. Gottesman said she agreed on not changing the sentence dealing with laboratory experiments. For large-scale experiments, she felt it important to maintain IBC oversight on a case-by-case basis. But she agreed that to strengthen this concept of latitude there should be a rewording of that statement and she suggested a statement such as:

"For large-scale (LS) fermentation experiments, the IBC shall review physical containment conditions. Generally conditions need be no greater than those for the host organism unmodified by recombinant DNA techniques. IBC review should include consideration of the description of BL1-LS in Appendix K-II."

Dr. Johnson stated that since Dr. Young was a previous member of the RAC and is knowledgeable in the molecular biology of B. subtilis, that the RAC should take his suggestions seriously. He then stated he took issue with Dr. McKinney's statement that there was no requirement for manufacturers to obey the NIH Guidelines in light of the fact that industry has indicated it will obey the NIH Guidelines voluntarily and that regulatory agencies insist upon it.

Dr. Johnson said that in the vast experience with E. coli, B. subtilis, and S. cerevisiae there have been no health associated risks involving large-scale production with these organisms except for occasional hypersensitivity to secondary metabolites in the fermentation process.

Dr. Johnson said that while he generally supported the thrust of the proposal, since the proposal came from an agency which regulates the company which employs him, he felt there could be an apparent conflict of interest and that he would like the public record to show that he would be abstaining from any vote on the proposal.

Dr. Sharples asked if the wording proposed by Dr. Young applied only to S. cerevisiae, B. subtilis, and E. coli, to which Dr. Talbot replied that that was the case. Dr. William Szkrybalo of the Pharmaceutical Manufacturers Association stated that his organization felt the proposed revisions were highly important clarifications of the NIH Guidelines. They will provide "appropriate consistency of policy and practice throughout the research process." He said that at present IBCs are reluctant to use the "some latitude" provision. He cited the industry's long and distinguished record in fermentation techniques. His organization supports Dr. Young's proposal and believes it will enhance the strategic planning process at member companies and the competitive position of U.S. biotechnology and pharmaceutical industries.

Dr. Miller said he would not have a strong objection to maintaining the original language where it describes containment at laboratory-scale, but that the important change is for large-scale and the proposed change for laboratory-scale was added for consistency.

Dr. McKinney noted that Section III-B-5 of the NIH Guidelines imposes upon the IBCs the obligation to establish the containment level for large-scale experiments. Dr. Gottesman underlined the fact that the proposal would not change the requirement for IBC review. She suggested not accepting the first sentence of Dr. Young's proposal, i.e., keeping the text as is for laboratory-scale experiments. For the large-scale experiments, she suggested accepting Dr. Young's proposal, but with the addition of the word "generally", i.e., "...conditions generally need be no greater..." She said the word "generally" would involve overall advice to the IBCs, but they could raise containment in specific cases if they believed it was indicated. Mr. Mitchell asked Dr. Gottesman if she meant this wording to apply to all three sections being discussed. She replied that she did.

Dr. Gottesman then moved that the RAC not accept the first sentence proposed by Dr. Young but accept the second sentence, modified to read:

> "For large-scale (LS) fermentation experiments, the appropriate physical containment conditions generally need be no greater than those for the host organism unmodified by recombinant DNA techniques."

Dr. Epstein seconded the motion, and Drs. Walters and McKinney said they supported it.

Dr. Vidaver suggested that the clause "provided that the new product is neither toxic nor allergenic to humans," might be added to the end of the sentence. Dr. Gottesman stated that if such cloning produced molecules which were highly toxic for vertebrates they would be covered under Section III-A-1 of the NIH Guidelines.

Dr. Cohen said that perhaps one could say:

> "The appropriate physical conditions are those consistent with good manufacturing processes as used for the host organism without recombinant DNA."

Dr. John Keene from Abbott Laboratories said that the RAC should be dealing with the safety associated with recombinant DNA, not the product. In industry, one looks at the safety of personnel and protecting them from any untoward effects regardless of the use of recombinant organisms.

Mr. Mitchell then asked Dr. Gottesman to state the current motion as amended for purpose of a vote. She stated the proposal is to change that paragraph in Appendices C-II, C-III, and C-IV which currently begins, "For large-scale..." to now read:

"For large-scale (LS) fermentation experiments, the appropriate physical containment conditions generally need be no greater than those for the host organism unmodified by recombinant DNA techniques."

The motion, being duly made and seconded, was approved by a vote of 13 in favor, none opposed, and 2 abstentions. It was noted that Dr. Johnson abstained from voting for reasons of potential conflict of interest.

VII. REPORT FROM THE HUMAN GENE THERAPY SUBCOMMITTEE

Mr. Mitchell then called on Dr. Walters to present the report from the Human Gene Therapy Subcommittee. Dr. Walters reported that the Lay Language Working Group had met in January and developed a plan of action for producing a document entitled, Oversight of Research Involving Human Gene Therapy for Human Patients: General Information. He noted that Ms. Ann Witherby, who could not attend today's meeting because of illness in her family, had provided a copy of the working group report which had been distributed to all RAC members. The document to be produced will probably have four parts including: a brief explanation of how gene therapy will work; discussion of the general oversight framework of the Federal Government; a lay language summary of the Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols; and information about other publications and films available to the public for further information. Dr. Walters said the Human Gene Therapy Subcommittee would review this document at its April 24, 1987, meeting and that it was anticipated to be brought before the full RAC for review at the next RAC meeting.

VIII. FUTURE MEETING DATES

Dr. Gartland noted the only future meeting date currently scheduled was for June 15, 1987.

IX. ADJOURNMENT

Having concluded the agenda and there being no further business to be discussed, Mr. Mitchell adjourned the committee at 3:25 p.m., on February 2, 1987.

William J. Gartland, Jr., Ph.D.
Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date: 9/21/87

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December 29, 1986

M E M O R A N D U M

To: Members
Recombinant DNA Advisory Committee

From: Executive Secretary

Subject: February 2, 1987, Meeting - Mailing I

The next meeting of the committee will be on February 2, 1987, at the National Institutes of Health, Building 1, Wilson Hall, 9000 Rockville Pike, Bethesda, Maryland 20892. The meeting will begin at 9 a.m. This will be a one day meeting.

Room reservations have been made for the evening of February 1, 1987, at the Bethesda Marriott Hotel (301-897-9400) for those of you who will need accommodations. If you wish to change or cancel these reservations, please contact Ms. Becky Lawson in my office at 301-496-6051. For arrival after 6 p.m., a deposit in the amount of one night's stay is required by either a check in the amount of $71 or a major credit card authorization. The hotel will not hold the room past 6 p.m. without a deposit.

Drs. Royston Clowes, Gerard McGarrity, and Robert McKinney will be attending the meeting as consultants.

A preliminary list of primary reviewers is included in this mailing.

Enclosed for your consideration are the following documents:

Proposal to modify Sections I-A and III-A of the Guidelines.....1283

Proposal to modify Appendices C-II, C-III, and C-IV of the Guidelines.....1284

Minutes of December 5, 1986, meeting of Working Group on Definitions.....1285

Notice of meeting and proposed actions.....1286

Please bring all these materials with you to the meeting.

William J. Cartland, Jr., Ph.D.

Enclosures

PRIMARY REVIEWERS

Dr. Cohen.....1284

Dr. Davis.....1283

Dr. Gottesman.....1285

Dr. Johnson.....1283

Dr. Korwek.....1283, 1285

Dr. McGarrity.....1284, 1285

Dr. McKinney.....1284

Dr. Pramer.....1285

Dr. Sharples.....1285

Dr. Vidaver.....1285

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